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Pleural infection

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A B S T R A C T

Pleural infection is a relatively common complication of pneumonia with a broad aetiology. Parapneumonic effusions caused by an infection of the pleural membranes occur in 40–57% of cases of pneumonia. A variable percentage (10–20%) of parapneumonic effusions progresses to empyema (pus) and/or abscess formation (encapsulation). Pleural infection is associated with significant morbidity and mortality. Diagnosis requires a multidisciplinary approach which may include respiratory physicians, thoracic surgeons, microbiologists and radiologists. Rigorous and prompt treatment with antibiotics, good clinical care and timely drainage of effusions remain the cornerstones of effective management.

Educational aims

- To discuss the aetiology and aetiopathogenesis of pleural infection.
- To point out the relative merits of various forms of treatment in pleural infection and the evidence base supporting them.
- To emphasize the importance of supportive care in the immunocompromised patient with pleural infection.
- To emphasize the importance of pleural fluid aspiration in the diagnosis and management of pleural effusions.
- To outline briefly current controversies in the management of empyema.

1. Introduction

Pneumonia (thought to be the chief aetiological process in the development of pleural space infection) is defined as an infection of the lung parenchyma with an estimated annual incidence rate of 5–11 cases per 1000 population, with around 50,000 hospital admissions in the UK per year.[1] Parapneumonic effusions caused by an infection of the pleural membranes occur in 40–57% of cases of pneumonia. A variable percentage (10–20%) of parapneumonic effusions progresses to empyema (pus) and/or abscess formation (encapsulation). Pleural infection is associated with significant morbidity and mortality which may be as high as 20–35% in immunocompromised patients.[2] Mortality in patients who develop empyema is associated strongly with the presence of co-morbidities. Diagnosis requires a multidisciplinary approach which may include respiratory physicians, thoracic surgeons, microbiologists and radiologists. Treatment of pleural infection involves antibiotics, supportive treatment and chest tube drainage although around 30% of patients fail to respond and require surgical intervention.[3]

2. Aetiology of pleural infection

Risk factors for the development of pleural infection include co-morbidities such as chronic lung diseases, rheumatoid arthritis, diabetes and substance abuse including alcoholism.[4] Those patients with a risk of aspiration pneumonia; substance abuse, neuromuscular disorders, seizures, mental retardation, GORD and those with poor dentition are known to have a tendency to develop anaerobic infections.[5] Infections are also more common in the immunocompromised, the very young and the elderly. Chest trauma and iatrogenic causes include surgery and thoracocentesis. For those patients with hospital acquired infections, the outcome is worse with an increased length of hospital stay of up to 2 months compared with community acquired infections which may be up to 2 weeks.[6]

Aerobic organisms are most commonly implicated in pleural infection. Streptococcal species are at the top of the list at around 60% (*Streptococcus milleri*, *pneumoniae*, *pyogenes* and others), followed by staphylococcal species (*Staphylococcus aureus*, MRSA) and Enterococcus at 15% of total infective causes. The gram-negative aerobes (*Escherichia coli*, *Klebsiella* sp., *Proteus* sp., *Pseudomonas* sp.) cause around 15% of identified pathogens and anaerobes (*Fusobacterium*, *Bacteroides*, *Clostridium*, *Mycobacterium TB* and *Actinomyces*) comprise 14%.[7] The organism responsible for the

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infection varies considerably between groups of patients. In community acquired empyema, 50% of cases in one series were due to streptococci and the remainder due to staphylococci, anaerobes and gram-negative bacilli.[8] For hospital acquired empyema (in association with hospital acquired pneumonia HAP), or iatrogenic causes, staphylococci, gram-negative bacilli, enterococcus species and MRSA (in around 20% of cases) are the organisms implicated. Patients with co-morbidities, especially diabetes or alcoholism, tend to develop gram-negative empyema. Some pulmonary parenchymal infections, caused by *S. aureus* and *Klebsiella pneumoniae*, are more likely to progress to pleural infections than others.[8] Fungi such as Candida and Aspergillus are increasingly common agents of fungal empyema. A large randomised, multicentre trial in pleural infection recently reported that microbiological diagnosis was reached in 57% of cases and an extra 16% were diagnosed using PCR. Blood cultures from patients were found to be positive in only 12% of cases but added significantly to the data as often this was the only positive result available.[8] In 15–20% of cases, no identifiable microbiological cause was found.

3. Pathogenesis of pleural infection

Pleural infection can be defined as a progressive process, whereby a self-resolving parapneumonic effusion may progress to a complex, multi-loculated fibrotic collection which requires surgical intervention. The pathophysiology of this process evolves through three distinct phases: the exudative phase, the fibrinopurulent stage and the organisational stage.[9] These stages reflect the changing physiology within the pleural space which may not always follow a linear fashion and is summarised by Light's Classification (Table 1).[10]

The exudative phase begins when inflammation of the lung parenchyma causes increased permeability of the pleural membranes. Transfer of interstitial fluid across the visceral pleura occurs. Pro-inflammatory cytokines (IL-6, 8 and TNF-alpha) enhance mesothelial permeability and increase vascular permeability, influenced by immune processes including neutrophil migration. This results in the formation of increased pleural fluid volume without bacteria (Table 2). Patients may complain of pleuritic chest pain which will generally resolve spontaneously with the correct antibiotic therapy.

The fibrinopurulent phase commences with bacterial invasion of the pleural space. Normal fibrinolytic activity is disrupted by the rise in PAI-1 and 2 (plasminogen activator inhibitor) and TNF-alpha which are directly released from mesothelial cells. Fibrin deposition results in the formation of fibrinous septae with fluid loculation and adhesions. This process, although part of the healing by invasion of fibrous tissue, often impairs the efficacy of chest tube drainage. The physiology of the pleural fluid changes as a result of bacterial wall-induced neutrophil phagocytic activity causing a rise in lactic acid and a fall in pH and glucose (Table 2). This stage initiates the point of transition to the infected state. Neutrophils infiltrate the pleural cavity, lactate dehydrogenase is produced and the fluid becomes frank pus due to bacterial and inflammatory cell lysis and death.

The organising stage is driven by PDGF, with TGF-beta causing proliferation of fibroblasts which form collagenous, inelastic, fibrous pleural scaring. This process impairs lung function as re-inflation of the lung is inhibited. At this stage chest tube drainage even with the use of fibrinolytics, will probably fail. Interestingly, the clinical course varies significantly between patients. Some patients do not develop significant pleural scarring; others develop chronic sepsis and significant lung deficits whereas some have spontaneous resolution of the pleural thickening and subsequent recovery.

Table 1
Light's Classification of pleural effusions.

Class	Description
Class1 – non-significant	<10 mm thick on decubitus radiograph
Class 2 – typical parapneumonic	>10 mm thick, pH > 7.2, glucose > 40 mg/dL.
Class 3 – borderline complicated	pH 7.0–7.2 or LDH > 1000, gram stain + culture negative
Class 4 – simple complicated	pH < 7.0, gram stain/culture positive, not loculated or frank pus.
Class 5 – complex complicated	pH < 7.0, gram stain/culture positive, multiple loculated.
Class 6 – simple empyema	Frank pus, single locule or free flowing.
Class 7 – complex empyema	Frank pus, multiple loculations.

4. Diagnosis of pleural infections

Clinically, patients with pleural infection present with symptoms of pneumonia. Commonly they experience acute onset cough, often productive of purulent sputum, fever, dyspnoea and may have pleuritic chest pain.[11] Anaerobic infections may present with non-specific features of anorexia, weight loss and malaise. Assessment of risk factors for suspected pneumonia often helps with diagnosis in these cases. No clinical features will reliably predict which patients with effusions will require drainage.[12]

Chest radiography is the mainstay of diagnostic imaging and can confirm the presence and size of a pleural effusion and/or consolidation. A pleural based mass or loculated area of fluid may be indicative of the presence of empyema. Pleural aspirate under ultrasound guidance is particularly useful in the case of small or loculated effusions. Contrast enhanced CT can differentiate pulmonary abscess from empyema when the "split pleural sign" is present (Fig 1). Pleural thickening is frequently seen in empyema and its absence may suggest other pathology.[15] MRI gives excellent detail of pleural fluid characteristics including the presence of septations, but cannot reliably differentiate between malignant and infective effusions.

All patients with pleural effusion in the context of clinical symptoms suggesting infection should have an aspirate of the fluid sent for microscopy, biochemistry and culture. If the effusion is small, the aspirate should be carried out under ultrasound guidance. The presence of frank pus in the aspirate is diagnostic of empyema.[9] A gram-positive stain or positive culture of a non-purulent aspirate is diagnostic of established pleural infection. In general, Light's criteria should be used to differentiate between an exudate (effusions and empyema) and transudate (other pathological process).

In non-purulent fluid, pleural fluid pH is the best indicator of whether an effusion is likely to be complicated and require drainage or is simple and likely to resolve spontaneously. Current guidelines recommend chest drainage in effusions with pH < 7.20 in the correct clinical context, and treatment with antibiotics alone with pH > 7.20. The effusion can be re-sampled if not responsive to treatment or the patient is deteriorating.[13] Samples for pH testing should be collected in a heparinised syringe and tested immediately using a blood gas analyser. If the sample is frank pus then the pH does not need to be tested, as a chest drain is required for the treatment of empyema, and the pH gives no useful further clinical information. Although pH is reliable in predicting the course of an effusion, acidic pH alone is not diagnostic of pleural infection. Other causes of pleural effusions may result in acidic effusion (see Section 5 below) and occasionally infections can cause an alkaline effusion (*Proteus* spp.).

Samples of pleural fluid should be sent for microscopy, culture and sensitivity and are positive in 60% of cases.[14] The use of blood culture bottles for inoculation to test for the presence of anaerobic organisms is still to be evaluated fully.

Table 2
Pleural fluid stage changes [after Ref. [7]].

Observation	Simple effusion	Complicated effusion	Empyema
Appearance	Turbid	Cloudy	Pus
Markers	pH > 7.3	pH < 7.2	–
	↑LDH	LDH > 1000 IU/L	
	Glucose > 60 mg/dL or pleural/serum ratio > 0.5	Glucose < 35 mg/dL	
Cell	Neutrophils < 10000/μL	↑ Neutrophils (>10000/μL)	–
Gram stain	Negative	May be positive	May be positive
Culture	Negative	May be positive	May be positive

5. Differential diagnosis of pleural infections

Pulmonary embolism (PE), bronchial/pleural malignancy, abdominal/pelvic malignancy, collagen vascular diseases and iatrogenic causes (drugs) can all mimic pleural space infection.

Patients with malignancy may present with anorexia, weight loss, fever and raised inflammatory markers. Radiology (especially contrast enhanced CT scan) may be helpful in confirming the diagnosis; pleural aspirate may clinch the diagnosis (with positive cytology) or be supportive (e.g. mesothelial cells only with no inflammatory cells). Five percent of rheumatoid arthritis sufferers have pleural involvement, predominantly males. In rheumatoid pleuritis the pleural fluid may be acidic, with low glucose levels. In these cases a history of joint disease and RhF positivity may lead to the diagnosis.[11]

Pleural sepsis secondary to oesophageal rupture can be confused with primary empyema, especially in the elderly or if there is no clear history of chest pain or vomiting. The pleural aspirate may show food debris, amylase of salivary origin and radiology may show hydropneumothorax.[24] A chylothorax or pseudochylous effusion can also lead to clinical confusion and thus, the aspirate should be analysed for the presence of cholesterol and triglycerides if there is clinical suspicion of these causes.

Patients with pulmonary embolism may present with fever, pleuritic chest pain and effusion, but effusion biochemistry will not be supportive of pleural infection. A CTPA may be required to eliminate/diagnose the PE, as pleural aspirate findings are non-specific.[25]

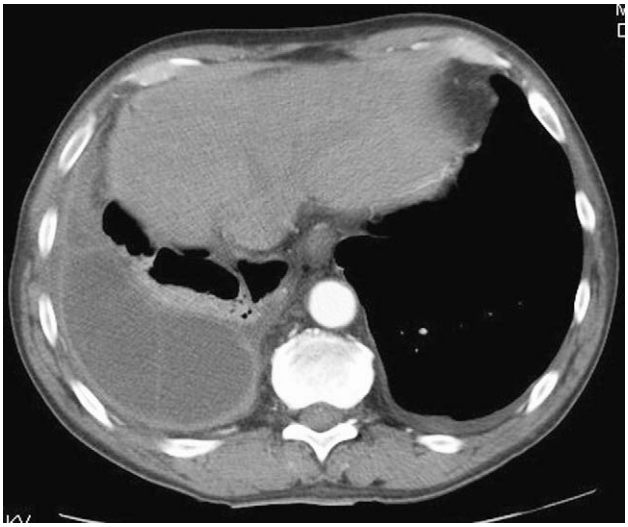

Fig. 1. The "split-pleura" sign (presence of contrast enhancement on both the visceral and parietal pleura, which are therefore clearly visible and separately visible due to the presence of pleural fluid – hence the name "split"). There are also a few septations within the pleural fluid – an unusual finding.

In pancreatitis, pleural fluid analysis may demonstrate raised amylase, and isoform analysis may be used to confirm pancreatic rather than salivary origin.

6. Management of pleural infections

Management of pleural infections comprises the general principles of treatment with antibiotics, attention to nutrition and supportive measures, with chest drainage or surgical intervention as necessary. Antibiotic therapy should be instigated as early as possible and empirical therapy commenced until microbial and biochemical results are available. Empirical therapy will be required in a significant number of cases for the duration of the illness, as pleural fluid cultures are negative for microorganisms in around 40%. In community acquired infections patients should be commenced on a second generation cephalosporin (cefuroxime) or aminopenicillin with beta-lactamase inhibitor (e.g. co-amoxiclav) plus anaerobic therapy (metronidazole).[16] In the penicillin-allergic, ciprofloxacin and clindamycin may be used. In hospital acquired infections, or those in whom iatrogenic empyema is likely or where MRSA is a major problem, a combination of a carbapenem and vancomycin will cover likely pathogens.[17] Local guidelines and sensitivities of organisms should be taken into account when determining therapy. Once investigation results are available, the regimen should be adjusted accordingly. Consideration should be given to continuing anaerobic cover, even in the absence of a positive culture, due to the culturing problems discussed above. Therapy should comprise 1 week of intravenous antibiotics and then oral formulations for at least 3 weeks. In the event of successful chest drainage, a shorter therapeutic time may be adequate.[18]

Insertion of chest drains of a smaller calibre (14 French) is associated with higher patient satisfaction due to less pain and mobility problems[19]; although larger drains continue to be advocated (>20 Fr).[20] The drain can be inserted under radiological guidance which allows insertion into the largest locule if a complicated pleural effusion is present and reduces the risk of inadvertent trauma to other organs. The efficacy of fibrinolytic agents to improve clinical outcomes is not confirmed in large studies and as such is not recommended as routine practice.[21] Further radiological imaging may be required if the effusion fails to resolve and position of the drain can be checked. Chest drains remain in place until clinical response dictates removal – they can be removed when the production of fluid reaches <150 ml/day.[22]

The indications and timing for surgical intervention have not been confirmed by good evidence, although patients who have had a few days of optimal therapy who are not improving should be discussed with an experienced surgeon.[23] First line surgical procedure for these patients is VATS (video assisted thoracoscopic surgery), although early evidence showed that 40% of cases will need to be converted to a formal decortication.[24] Excellent recovery results are shown after decortication in 95% of patients. However, complications can be significant. In some cases, slow withdrawal of drainage therapy over

months can lead to significant risks from pneumothorax and respiratory failure.

7. Summary

Pleural infection is a relatively common complication of pneumonia with a broad aetiology. The pathogenesis of the infection can be divided into a number of stages, each of which has a slightly different treatment algorithm. Investigation and management of pleural infection are contingent on careful imaging and aspiration of any effusion present. Rigorous and prompt treatment with antibiotics, good clinical care and timely drainage of effusions remain the cornerstones of effective management. Many of the processes accepted as dogma in the care of pleural infection are based on empiricism and there remains much scope for research in this important cause of morbidity in the population.

Conflict of interest statement

The authors have no conflict of interest.

CME Section

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Educational questions

Answer the following questions:

1. Which are the most commonly implicated organisms in pleural infection in the community?
   a. Streptococci
   b. Staphylococci
   c. *Pseudomonas* spp.
   d. *Fusobacterium* spp.
   e. Mycobacteria

2. According to current treatment guidelines, pleural effusions should be drained if the pH is:
   a. >7.20
   b. >7.50
   c. <7.20
   d. >7.40

3. All of the following can cause pleural effusions EXCEPT:
   a. Pulmonary embolism
   b. Heart failure
   c. Rheumatoid arthritis
   d. Osteoarthritis
   e. Abdominal malignancy with ascites

4. Pleural fluid cultures are negative for microorganisms in what number of cases?
   a. 30%
   b. 70%
   c. 90%
   d. 40%
   e. 10%

5. In community acquired pleural infections, patients should be commenced on which of the following antibiotics initially?
   a. Ciprofloxacin alone
   b. Vancomycin alone
   c. Ticarcillin and tobramycin
   d. Meropenem and metronidazole
   e. A second generation cephalosporin and metronidazole

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